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Thrombolysis in massive and submassive pulmonary embolism during pregnancy and the puerperium: a systematic review

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Abstract

Thrombolysis in high-risk pulmonary embolism (PE) patients is recommended worldwide; however, the evidence for thrombolysis during pregnancy and the immediate puerperium remains unclear. We conducted a systematic review from 1950 to 2019 through PubMed, Ovid/Willey, and Cochrane Library to assess the safety and effectiveness of thrombolysis during pregnancy and the immediate puerperium. Additionally, we characterized the clinical presentation, risk stratification, and diagnostic approach. We have communicated our results according to the PRISMA statement. We collected 141 records and, after critical assessment, included 47 case reports of 54 patients, including 43 and 11 patients during pregnancy and puerperium, respectively. During pregnancy, alteplase was the most frequent systemic thrombolytic agent used (67%), but only nine patients received the approved FDA regimen. With catheter-directed thrombolysis, low-dose thrombolytics and fragmentation were the most common regimens. Major bleeding occurred in 18% of cases, but there was no intracranial bleeding. One maternal death occurred secondary to refractory cardiogenic shock. Fetal mortality was 20%. During the immediate puerperium, nine patients received "off-label" first-, second-, and third-generation thrombolytic regimens, and four cases underwent catheter-directed thrombolysis. We observed nine major bleeding events, seven of which were from the uterine location and none of which were intracranial. In conclusion, overall, these data do not suggest prohibitive risk associated with thrombolysis for PE in pregnancy. Management of massive and high-risk submassive PE in pregnancy should be individualized to each patient. In the data presented, no fatal bleeding or intracranial bleeding was observed. Finally, future efforts should systematically collect and report data on high-risk PE in pregnancy and peripartum patients to improve the evidence-base clinical practice.

Keywords Pulmonary embolism · Thrombolytic therapy · Pregnancy · Puerperium · Peripartum · Postpartum · Systematic review

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Highlights

- Overall, these data do not suggest prohibitive risk associated with thrombolysis for PE in pregnancy. Although, catheter-directed thrombolysis could be an alternative, further research is mandatory.
- Uterine hemorrhages were the main complication related to thrombolysis, especially during puerperium.
- A multimodal diagnosis approach including bedside echocardiogram, doppler ultrasound, and cardiac biomarkers could optimize clinical decision-making.
- Based on current evidence, international societies should advocate for a standardized framework to guide diagnosis and management of this high-risk population.

Introduction

Pulmonary embolism (PE) remains the third most frequent cause of cardiovascular mortality after ST-elevation myocardial infarction and stroke. It is the main cause of pregnancy-related maternal death in developed countries [1, 2]. Based on current data, the mortality rate from PE is estimated to be 1.1 to 1.5 per 100,000 deliveries in the United States and Europe, and in the United Kingdom, venous thromboembolism accounts for one-third of maternal deaths [3]. Although global guidelines [4–8] recommend thrombolysis for patients with clinical instability and severe right ventricular dysfunction, recommendations for pregnancy are scarce or even absent [5–8]. Because decision-making is a challenge, we performed a systematic review that was focused on mechanical and systemic thrombolysis in massive and submassive PE during pregnancy and the immediate puerperium. We also analyzed clinical presentations, risk stratification, diagnostic approaches, bleeding complications, and obstetrical and neonatal outcomes in this population.

Methods

We searched for systematic reviews, cohorts, case series, case reports, editor letters, and abstracts related to pregnancy or to the immediate puerperium according to the PRISMA statement [9]. The objective was to assess the safety and effectiveness of systemic thrombolysis, catheter-directed thrombolysis (CDT) or catheter-directed ultrasound-assisted thrombolysis (CDUAT) in pregnant-puerperium PE patients. Additionally, we analyzed the clinical presentation, risk stratification, and diagnostic approach. We limited the immediate puerperium to the first 48 h after delivery to evaluate bleeding as a side effect. We included PE that was confirmed by VQ lung scan, angio-CT or pulmonary angiography. We excluded air and amniotic fluid embolism. The outcomes of interest were the safety and effectiveness of thrombolysis and the morbidity and mortality rates of the mothers and newborns.

We performed a systematic review of data from 1950 to 2019 through PubMed, Ovid/Willey, and the Cochrane Library. The search strategies used are provided in the supplementary appendix. We used the snowballing method [10], a manual search to avoid lost reports, and no language restriction. Investigators were not blinded to the journal, author, or institutions.

We identified potentially eligible studies by examining titles and abstracts. Full articles were obtained to assess eligibility criteria before the critical appraisal. We extracted cases that met the eligibility criteria from previously published systematic reviews. Data extraction of every case report was performed and analyzed by all investigators to ensure quality data extraction. The authors were trained regarding PE by an expert cardiologist (C.JS.). We had meetings to discuss extracted data and resolve disagreements. For the primary analysis of pregnant PE patients, the main variables were maternal and gestational age, thrombolytic agent, maternal outcome and fetal/neonatal outcome; we also analyzed complications related to thrombolysis. During the immediate puerperium, the main variables were maternal age, the timing for thrombolysis after delivery, thrombolytic agent, maternal outcome and complications associated with thrombolytic therapy. For those cases with successful treatment without complications, we assumed a favorable outcome. For the secondary analysis of the PE diagnostic approach, from each case, we extracted information related to clinical presentation, symptoms, vital signs, electrocardiogram, chest X-ray, imaging tests pre- and post-thrombolysis, and biomarkers. Additionally, we analyzed the anticoagulation approach, outcome, treatment escalation, and reperfusion criteria. We established three groups: pregnancy and systemic thrombolysis, pregnancy and CDT or CDUAT, and puerperium under systemic thrombolysis and CDT or CDUAT. Major bleeding was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 2 g/dL (1.23 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells [11]. Other definitions, including massive PE and successful thrombolysis, are available in the supplementary appendix.

Statistical methods

We used summary statistics for continuous and categorical variables according to their types and distributions. For categorical variables, we report the frequency and percentage (n > 20), and for continuous variables, we report the median and interquartile range (25th percentile to 75th percentile). No hypothesis testing was performed, given the quality of the information obtained. All data were analyzed using GraphPad (GraphPad Software, Inc., CA, USA).

Results

We carried out the systematic review until December 10, 2019. Figure 1 shows the flowchart, including the four phases of PRISMA, and obtained, eliminated, and excluded duplicated records. In the identification phase, we obtained 141 records from PubMed, Ovid/Willey, and the Cochrane Library. We extracted evidence for this review from 47 case reports, two case series, and two systematic reviews, with the first case report published in 1972.

Pregnancy and systemic thrombolysis

The pregnant PE patients were in the fourth decade of life (median age 33 [27–36] years), and one patient died. A total of 31 (78.4%) newborns were healthy at delivery. Table 1 [12–43] shows the baseline characteristics of the patients, including age, gestational weeks, the regimens used for systemic thrombolysis, the outcomes of the mothers and newborns, complications and the levels of evidence. Among the pregnant patients submitted to systemic thrombolysis, 24 had massive PE, and 13 had submassive PE. In most cases, acute events occurred during the second or third trimesters. Alteplase was the most frequent thrombolytic agent used in 25 patients (67%) (Table 1) in as follows: nine patients received 100 mg with the 2-h FDA approach (27%) [8], two patients (5.4%) received 50 mg over 2 h, and three patients (8.1%) received low doses (10 mg/h over 4 h plus 2 mg/h over 1.5 h, 25 mg over 3 h, and a 10-mg bolus plus 40 mg over 2 h) [13, 22, 30, 40]. The remaining patients were treated with the alteplase "off-label" regimen based on different doses and infusion ranges (90 min to 8 h) (Table 1). Other regimens were low-dose and long-term streptokinase and urokinase infusion in nine patients (33%), three patients received monteplase (8.1%) and one received tenecteplase (2.7%) (Table 1). Obstetric complications included seven major bleedings (18%), four uterine hemorrhages (10%), one patient presented traumatic hematomas (2.7%), and one placental hemorrhage related to intraoperative monteplase (2.7%). Major bleeding occurred in four patients with low-dose and long-term streptokinase infusions (10.8%), two patients with monteplase (5.4%), and two with "off-label" alteplase in continuous infusions (5.4%) (Table 1). We did not find any case intracranial hemorrhage. One maternal death occurred secondary to refractory cardiogenic shock [31]. Eight fetal deaths (20%) occurred related to hypoxemia secondary to maternal cardiogenic shock, respiratory distress, and infection [12, 27, 28, 38, 39].

Pregnancy and catheter-directed thrombolysis

The most frequent therapeutic approach was low-dose first- and second-generation thrombolytics plus catheter fragmentation. Alteplase was frequently used in several low-dose regimens (Table 2) [44–49]. Two patients had massive PE, and four had submassive PE. Only one case with successful CDUAT was identified. We observed one case with major bleeding (hemoglobin < 2 g and spontaneous abortion) [45]. No intracranial or uterine hemorrhage was reported. The characteristics of the catheters were reported for only three cases [38, 39, 42] (Table 2).

Puerperium

The patients were young, and in most cases, the event occurred immediately or within the next few hours after delivery. The main baseline characteristics are provided in Table 3 [50–60]. Eleven patients with massive PE and three with submassive PE received systemic thrombolysis without mortality. Nine patients were under "off-label" first-, second-, and third-generation thrombolytic regimens; eight of them had major bleeding, and seven had major bleeding from the uterine location. Two patients undergoing CDT had fewer bleeding complications and better outcomes. We did not identify any case of intracranial hemorrhage. One patient died secondary to multiple organ failure on day 116 [57] (Table 4).

Clinical presentation, diagnostic approach, and biomarkers

The main characteristics of 54 PE pregnant and puerperium patients are shown in Table S1. The clinical presentation was driven by tachycardia and dyspnea alone or associated with chest pain. Patients who underwent systemic thrombolysis had severe hypotension and hypoxemia compared with those who underwent CDT. In the puerperium group, BP and oximetry data were not available (Table S1). In all groups, > 40% of cases had deep venous thrombosis or cardiogenic shock. Despite clinical conditions, patients received intravenous fluids and different regimens of unfractionated heparin for several hours before thrombolysis. The electrocardiogram and chest X-ray percentages are shown in Table S1. A high clinical suspicion, clinical instability, and

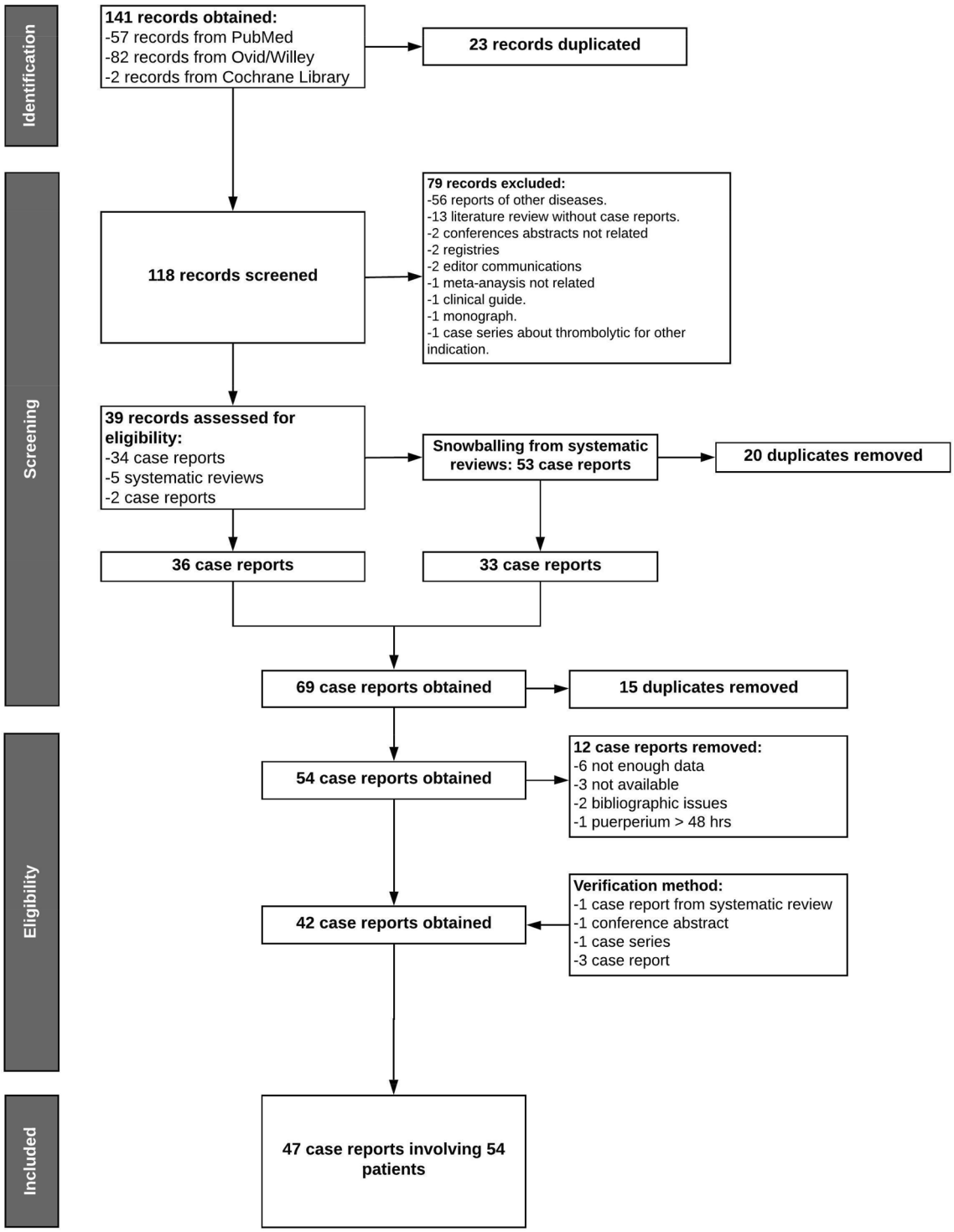

Fig. 1 PRISMA flow diagram

echocardiography findings drive thrombolysis in a high proportion of pregnant and puerperium PE patients. The proportion of biomarkers for risk stratification (troponin and BNP) and diagnosis (D-dimer) was low (Table S1). The diagnostic approach was angio-CT scan in nine patients (27%), seven used V/Q scan (21%), and three pulmonary angiography (10%) in the PE pregnant group treated with systemic thrombolysis, and in patients under CDT, the diagnosis was made by pulmonary angiography. In the puerperium group, a V/Q lung scan was performed in four cases, angio-CT was

Table 1 Thirty-seven pulmonary embolism pregnant women submitted to systemic thrombolysis

Author, year	No. pts	Age	Gestational Weeks	Thrombolytic	Regimen	Outcome mother/ newborn	Complications	LoE
Massive pulmonary embolism (24 pts)								
Baudo et al., 1990 [12]	1	29	35	rt-PA	100 mg/3 h	Good/Death	Preterm delivery	5
Floßdorf et al., 1990 [13]	1	27	31	UK & rt-PA	UK 200,000 bolus failure and then rt-PA: 10 mg/h/4 h, infusion 2 mg /h/1.5 h	Good/Good	Preterm delivery. Minor bleeding	5
Kramer, 1995 [14]	1	20	21	UK	Bolus 4,400 U/kg /10 m, then infusion 4,400 U/k/h/12 h	Good/Good	No	5
Saviotti, 1997 [15]	1	33	3rd Trim	rt-PA	Bolus 50 mg /5 m, after 30 min, 50 mg infusion/60 m followed by 75 mg	Good/Good	Major bleeding, uterine bleeding	5
Horak et al., 1999 [16]	1	37	8	rt-PA	100 mg /2 h	Good/Good	No	5
Ahearn GS, 2002 [17]	1	36	12	rt-PA	100 mg /2 h	Good/Good	No	1, 5
Yap L, 2002 [18]	1	28	30	rt-PA	Bolus 10 mg, 90 mg /2 h	Good/Good	No	5
Trukhacheva, 2005 [19]	1	34	23	rt-PA	Bolus 10 mg and then, 90 mg/90 min	Good/Good	No	5
Jensen et al., 2009 [20]	1	33	29	rt-PA	NA	Good/Good	No	5
Te Raa, 2009 [21]	1	34	25	SK	Bolus 250,000 U then infusion 100,000 IU/h/24 h	Good/Good	Major bleeding, traumatic hematomas	1,5
Biteker, 2010 [22]	1	21	35	rt-PA	25 mg/3 h	Good/Good	No	5
Fasullo, 2011 [23]	1	26	24	rt-PA	Bolus 10 mg bolus then 90 mg /2 h	Good/Good	No	5
Holden, 2011 [24]	3	44[a] 27[b] 33[c]	25[a] 11[b] 8[c]	SK[a] / rt-PA[2,3]	Bolus 250,000 IU then 100,000 IU/h/24 h[1] rt-PA bolus 10 mg/90 mg/2 h[b,c]	Good/Good Good/Good Good/Good	No	4
Lonjaret et al., 2011 [25]	1	33	31	rt-PA	Bolus 10 mg then 90 mg/ 90 min	Good/Good	Minor bleeding	5
Dos Santos et al., 2012 [26]	1	37	29	TNK	Bolus 40 mg/5 min	Good/Good	No	5
Tawfik et al., 2013 [27]	1	29	3rd trim	SK	Bolus 250,000I U/30 m then 100,000 U/h/12 h	Good/Death	No	5
Albasha et al., 2014 [28]	1	28	15	rt-PA	NA	Good/Death	No	5
Epperla et al., 2015 [29]	1	26	13	rt-PA	50 mg after returned spontaneous circulation	Good/Death†	No	5
Liao et al., 2018 [30]	1	26	10th	rt-PA	Bolus 10 mg then 40 mg/2 h	Good/Death	Mild-severe hematuria	5

Table 1 (continued)

Author, year	No. pts	Age	Gestational Weeks	Thrombolytic	Regimen	Outcome mother/ newborn	Complications	LoE
Ben Halima et al., 2018 [31]	2	28 32	8 36	rt-PA rt-PA	Bolus 10 mg then 90/ 90 min Bolus 10 mg then 90 mg/90 min	Good/Good Death/Unknow	No Refractory cardiogenic shock	4
Miyoshi et al., 2019 [43]	1	39	28	Monteplase	240,000 units IV 16 min after delivery*	Good/Good	Major bleeding	5
Submassive pulmonary embolism (13 pts)								
Hall et al., 1972 [32]	1	29	32	SK	600,000 IU in 90 min and 100, 000 IU/h/ 41 h	Good/Good	Preterm delivery, major bleeding, uterine hemorrhage	5
Delclos et al., 1986 [33]	1	19	28	UK	4400 U/kg/10 min, infusion of,400 U/k/h/12 h	Good/Good	Minor bleeding	5
Fagher et al., 1990 [34]	1	21	28	SK	100,000 IU/30 m, then 100,000 U/h/10 h	Good/Good	Preterm delivery, major bleeding, uterine hemorrhage	5
Seifried et al., 1991 [35]	1	30	11	rt-PA	20 mg /20 min, followed by two infusions of 20 mg/8 h	Good/Good	No	5
Mazeika et al., 1994 [36]	1	34	25	SK & F	200,000 IU/20 min and then 100, 000 U/h/12 h	Good/Good	Major bleeding, uterine hemorrhage	5
Patel et al., 2003 [37]	1	36	20	rt-PA	Bolus 10 mg, 90 mg /2 h	Good/Good	No	5
Varsano et al., 2008 [38]	1	39	11	rt-PA	100 mg/ 2 h	Good/Death	No	5
Samejima et al., 2013 [39]	1	40	28	Monteplase	21,000 U/kg Intraoperative	Good/Death	Major bleeding, placental hemorrhage	5
Dhutia et al., 2014 [40]	1	37	34	rt-PA	Bolus 10 mg then 40 mg/2 h	Good/Good	No	5
Açar et al., 2015 [41]	1	36	27th	rt- PA	Bolus 10 mg then 90 mg/2 h	Good/Good	No	5
Oami et al., 2018 [42]	1	37	23th	Monteplase	Bolus 800,000 U then 800,000 U 30 min after first dose	Good/Death	No	5
Ben Halima et al., 2018 [31]	2	38 26	36 19	rt-PA rt-PA	100 mg IV 100 mg IV	Good/Good Good/Good	No	4

SK streptokinase; *UK* urokinase; *rt-PA* recombinant tissue plasminogen activator type alteplase; *TNK* tenecteplase; *LoE* level of evidence; (1) systematic review; (4) case series; (5) case reports; [a]Patient 1; [b]Patient 2; [c]Patient 3. †Death at 25th week. *3 days after thrombolysis the patient went to CF

performed in four cases, and pulmonary angiography was performed in three cases.

Bleeding complications and mortality

The main clinical outcomes related to hemorrhage and maternal and high fetal mortality are shown in Table S2.

We identified the lowest incidence of major bleeding complications in pregnant PE patients undergoing CDT. The high proportion of major hemorrhage was driven by systemic thrombolysis and uterine bleeding in the puerperium patients. Only one maternal death occurred and was secondary to refractory cardiogenic shock [31].

Table 2 Catheter-directed thrombolysis and catheter-directed ultrasound-assisted thrombolysis in pregnancy pulmonary embolism patients

Author, year	No. Pts	Age	Gestational Weeks	Thrombolytic	Regimen	Outcome mother/ newborn	Complications	LoE
Massive pulmonary embolism								
Krishnamurthy et al., 1999 [44]	1	31	26	UK	2,200 U bolus/kg, Infusion 2,200U/ kg/h	Good/Good	No	5
Sofocleous et al., 2001 [45]	1	19	15	CF[1], rt-PA	Bolus 10 mg, then infusion 2 mg/h/12 h	Good/Death	Major bleeding, Spontaneous abortion after 24 h	5
Submassive pulmonary embolism								
Bechtel et al., 2005 [46]	1	29	30	CF[2] rt-PA	12 mg in 60 ml normal saline, followed by 0.7 mg/h/5 h	Good/Good	No	5
O'Keefee et al., 2008 [47]	1	40	38	CF and CA/rt-PA	50 mg/3 h followed by infusion of 1 mg/h	Good/Good	Hematoma at episiotomy site	5
Pick et al., 2015 [48]	1	34	33	rt-PA	6 mg in each infusion catheter followed by 0.5 mg/h	Good Good	No	5
Kalathiya et al., 2017 [49]	1	23	12	US[3] + rt-PA	2 mg bolus, 0.5 mg infusion/ h/24 h	Good/Good	No	5

Pts patients; *UK* urokinase; *CF* catheter directed thrombolytic therapy plus mechanical fragmentation; *rt-PA* recombinant tissue plasminogen activator; *CA* catheter aspiration; (1) Mewissen infusion catheter (Boston Scientific, Quency, MA); (2) 5F vertebral catheter (Cook Medical Inc, Blooming, IN); (3) Ekos ultrasound catheter system (EKOS Corporation, Bothshell, WA); LoE: level of evidence; (5) case reports

Table 3 Immediate puerperium high-risk PE submitted to systemic thrombolysis

Author, year	No. Pts	Age	Timeline for PE after delivery	Thrombolytic	Regimen	Outcome mother	Complications	LoE
Massive pulmonary embolism								
Arlt et al., 2009 [50]	1	27	4 h	TNK	5 mg /15 min	Good	Major bleeding, endotracheal and uterine hemorrhage. Required hysterectomy	5
Azarisman et al., 2010 [51]	1	35	4 h	TNK	30 mg	Good	Major bleeding, uterine hemorrhage. Required blood transfusions 1800 ml	5
Wenk et al., 2011 [52]	1	34	19 min	Reteplase	10 U, followed by 10 U /30 min intraoperative	Good	Major bleeding, uterine hemorrhage. Required transfusion 2100 ml	5
Leeper et al., 2013 [53]	1	30	29 min	rt-PA	2 doses of 50 mg	Good	Major bleeding, uterine hemorrhage. Required laparotomy	5
Sitkin et al., 2013 [54]	1	30	After elective caesarian section	SK	NA	Good	Major bleeding, uterine hemorrhage 20 min after the administration. Required hysterectomy	5
Shaulov et al., 2014 [55]	1	36	48 h	rt-PA	50 mg after 30 min at cardiac arrest & a further 50 mg 15 min later	Good	Major bleeding, uterine hemorrhage. intramuscular rectus hematoma with free intra-abdominal blood. Required hysterectomy	5
Submassive pulmonary embolism								
Nishimura et al., 1998 [56]	1	35	Immediately after cesarean section	rt-PA	3 mg followed by infusion 20 mg/h intraoperative	Good	Major bleeding, uterine hemorrhage and abdominal incision, multiple transfusions in next 35 h	5

SK streptokinase; *rt-PA* recombinant tissue plasminogen activator type alteplase; *TNK* tenecteplase; *PA* pulmonary artery; *CA* catheter aspiration; *LoE* level of evidence; (5) case reports

Table 4 Immediate puerperium high-risk PE submitted to catheter- directed thrombolysis

Author, year	No. Pts	Age	Timeline for PE after delivery	Thrombolytic	Regimen	Outcome mother	Complications	LoE
Massive pulmonary embolism								
Onoyama et al., 1996 [57]	1	30	24 h	rt-PA + UK	6 million U in 10 min in PA, followed by 18 million U IV in 40 min + UK (360×10^3U/24) [3.5 h after rt-PA]	Death	Major intra-abdominal bleeding Required transfusion. Multiple organ failure on 116th day	5
Submassive pulmonary embolism								
Aya et al., 1999 [58]	1	20	48 h	Catheter directed rt-PA	57 mg /6 h	Good	Minor bleeding at the puncture site	5
Weinberg et al., 2011 [59]	1	27	Immediately after hemodynamic stabilization	Catheter directed CA UK	300,000 U, directly into the clot, followed by infusion at 100,000 U/h/24 h	Good	Multiple organ failure	5
SBP not specified								
Watanabe et al., 1995 [60]	1	29	48 h	UK	NA	Good	No	5

rt-PA recombinant tissue plasminogen activator type alteplase; *UK* urokinase; *PA* pulmonary artery; *CA* catheter aspiration; *LoE* level of evidence; (5) case reports; *SBP* systolic blood pressure

Discussion

The main observations of this systematic review were: First, overall, these data do not suggest prohibitive risk associated with thrombolysis in pregnancy and puerperium. Second, although the FDA alteplase regimen [8] in pregnancy and CDT in the immediate puerperium could be alternative therapeutics, future research is needed to test these regimens. Third, in the immediate puerperium, major uterine hemorrhage emerges as the most feared hemorrhagic complication. Finally, in most cases, the acute event occurred during the second or third trimester, and the same clinical presentation was observed in nonpregnant submassive and massive PE patients [61–65].

Anticoagulation is the foundation of PE treatment. However, in patients with clinical instability, anticoagulation alone might not be enough, given the lack of fibrinolytic activity [66]. Thrombolysis may improve the mortality rate and outcomes of massive PE patients [67]. In sub-massive PE, whether thrombolysis improves outcomes sufficiently to justify the associated bleeding risk is less clear. In the PEITHO trial, full-dose thrombolysis conferred hemodynamic benefit at the expense of increased intracranial hemorrhage [68]. In trials of reduced-dose systemic thrombolysis and catheter-directed thrombolysis, bleeding risk has appeared more favorable [69, 70]. Despite high maternal mortality related to PE [71], current guidelines provide weak recommendations on thrombolysis in these populations [4–8]. This could explain why most patients received "off-label" regimens (73%) compared with the recommended FDA alteplase dose [4–8] (27%) % [16–18, 23, 37, 38, 41] (Table 1). Additionally, it is possible that physicians in charge had the perception of having fewer major bleeding complications [13, 22]. We do not observe any difference between the half-dose alteplase regimen (50 mg over 2 h) and 100 mg over 2 h. Low-dose alteplase plus fragmentation was a frequent therapeutic approach in most CDT PE patients [44–48] (Table 2). Considering current evidence with CDUAT, more evidence is required before its use can be extended in this population. Despite the current European guidelines and recommendations [8], pregnant submassive PE patients were under systemic or CDT (Table 1), it is possible that physicians in charge considered pregnancy to be a life-threatening risk factor. In newborns, the absence of bleeding complications suggests that heparins and thrombolytics do not cross the placenta, so although uterine bleeding is possible, fetal bleeding is not a complication of these therapies [17, 21, 72]. The high mortality of newborns (20%) was mainly observed in patients with massive PE and delayed therapeutic decisions prolonging the right ventricular dysfunction state [12, 27, 29, 30, 42]. In the immediate puerperium, most cases were treated with several thrombolytic regimens including

complicated clinical settings (intraoperative) [50–56, 60] (Table 3).

In this population intracranial hemorrhage was absent and uterine hemorrhage was the most common major bleeding complication, especially in the immediate puerperium, and was probably related to physiological uterine involution [73] (Table S2). In 93 nonpregnant submassive and massive PE patients under a one-hour streptokinase or alteplase infusion or tenecteplase regimen [61–65], the major bleeding locations were extrauterine. Despite low evidence, the association with fewer bleeding complications suggests that low-dose alteplase (20 mg) plus fragmentation seems to be a possible therapeutic option.

In most case reports, no risk factors are described, except for pelvic thrombophlebitis [31] and in two puerperium patients (cesarean section), but the absence of evidence is not evidence of absence. Additionally, it is possible to consider hereditary thrombophilia and immunothrombosis as alternative mechanisms [74][75]. The high-clinical suspicion (Table S1) was driven by sudden dyspnea, syncope, or chest pain in PE patients in the 2nd or 3rd trimester. The clinical presentation was not different from that observed in nonpregnant patients [61–65]. There was a trend in a high proportion of massive PE patients to start with unsuccessful unfractionated heparin regimens,[8, 76]. In most patients the bedside echocardiogram drove thrombolysis and the use of biomarkers was low, despite its role in risk stratification [4–8]. The use, D-dimer to exclude PE is controversial, given its progressive increase and interindividual variability, and these values return to normal between days 30 and 45 after delivery [77]. Previous evidence suggested that plasma measurements of BNP $\leq$ 100 pg/mL in pregnant women with cardiac diseases had a negative predictive value of 100% for identifying cardiovascular maternal adverse events during pregnancy [78]. This finding suggests that this cut-off value could exclude the presence of right ventricular dysfunction in pregnant and puerperium patients. Moreover, cardiac troponin expression has no relationship with pregnancy or puerperium [79]; therefore, abnormal values could establish the difference between isolated right ventricular dysfunction with ischemia or right ventricular infarction [80]. Finally, the high proportion of deep venous thrombosis suggests lower limb ultrasound as an important alternative bedside tool in patients with severe clinical instability or unavailable diagnosis imaging tests.

Although several previous well-conducted systematic reviews have shown evidence for thrombolysis in this population [17, 21, 72, 81–85], our systematic review focused on clinical presentation, diagnostic approach, risk stratification, and treatment regimens for pregnant and puerperium patients who were previously overlooked.

The limitations of this study were as follows. This systematic review encompasses 47 years of substantial changes in the risk stratification and therapeutic approach of PE; additionally, descriptions of anticoagulation regimens, biomarkers, and positive outcomes are mostly limited to case reports and case series [86]. We advocate for the use of CARE guidelines to improve the quality of case reports. Our results confirm that the evidence for thrombolysis in this population is based on a summary of case reports [17, 21, 72, 81–85], Finally, a potential loss of reports from search engines is possible. Therefore, as has been previously considered, we also support an international registry for pregnant and puerperium patients undergoing thrombolysis or mechanical reperfusion to collect more information about thrombolysis in PE pregnant and puerperium patients [84].

In conclusion, overall, these data do not suggest prohibitive risk associated with thrombolysis for PE in pregnancy. Management of massive and high-risk submassive PE in pregnancy should be individualized to each patient. In the data presented, no fatal bleeding or intracranial bleeding was observed. Finally, future efforts should systematically collect and report data on high-risk PE in pregnancy and peripartum patients to improve the evidence-base clinical practice.

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Compliance with ethical standards

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